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STUDY PROTOCOL

Rationale and Design of ACO-REAL: A Real-World Non-Interventional Study of Acoramidis in Routine Clinical Practice

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ABSTRACT

***Introduction*:** Acoramidis, an oral transthyretin stabilizer that achieves near-complete stabilization, is approved for the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) based on the phase 3 study, ATTRibute-CM (NCT03860935). To complement trial data, ACO-REAL (NCT07235462) was designed to generate real-world evidence on acoramidis use in ATTR-CM. This article describes the rationale and design of ACO-REAL.

***Methods*:** ACO-REAL is an ongoing, prospective, non-interventional, multicenter study planned in approximately 2000 adults with ATTR-CM (wild-type or variant) initiating treatment with acoramidis in real-world settings across 21 European countries. The primary objective of ACO-REAL is to assess the characteristics and treatment patterns of participants with ATTR-CM receiving acoramidis during an observational period of around 12 months.

***Planned outcomes*:** The primary objective is to assess demographics (including age and sex), disease characteristics, and treatment patterns

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of participants treated with acoramidis. Disease characteristics include type, diagnosis, and manifestations of ATTR-CM, and ATTR-CM-relevant comorbidities. Treatment patterns include adherence, persistence, and reasons for treatment modifications, including switching from a different ATTR-CM medication to acoramidis. The secondary objective is to describe the safety profile of acoramidis. The clinical course of ATTR-CM in participants initiating acoramidis is also being evaluated through measuring cardiac function, functional capacity and health status (New York Heart Association classification and 6-min walk distance), and health-related quality of life (Kansas City Cardiomyopathy Questionnaire and EuroQol 5-Dimension 5-Level questionnaire). Healthcare resource utilization is also being evaluated. Statistical analyses will be exploratory and descriptive. Categorical variables will be presented as frequencies and continuous variables as sample statistics.

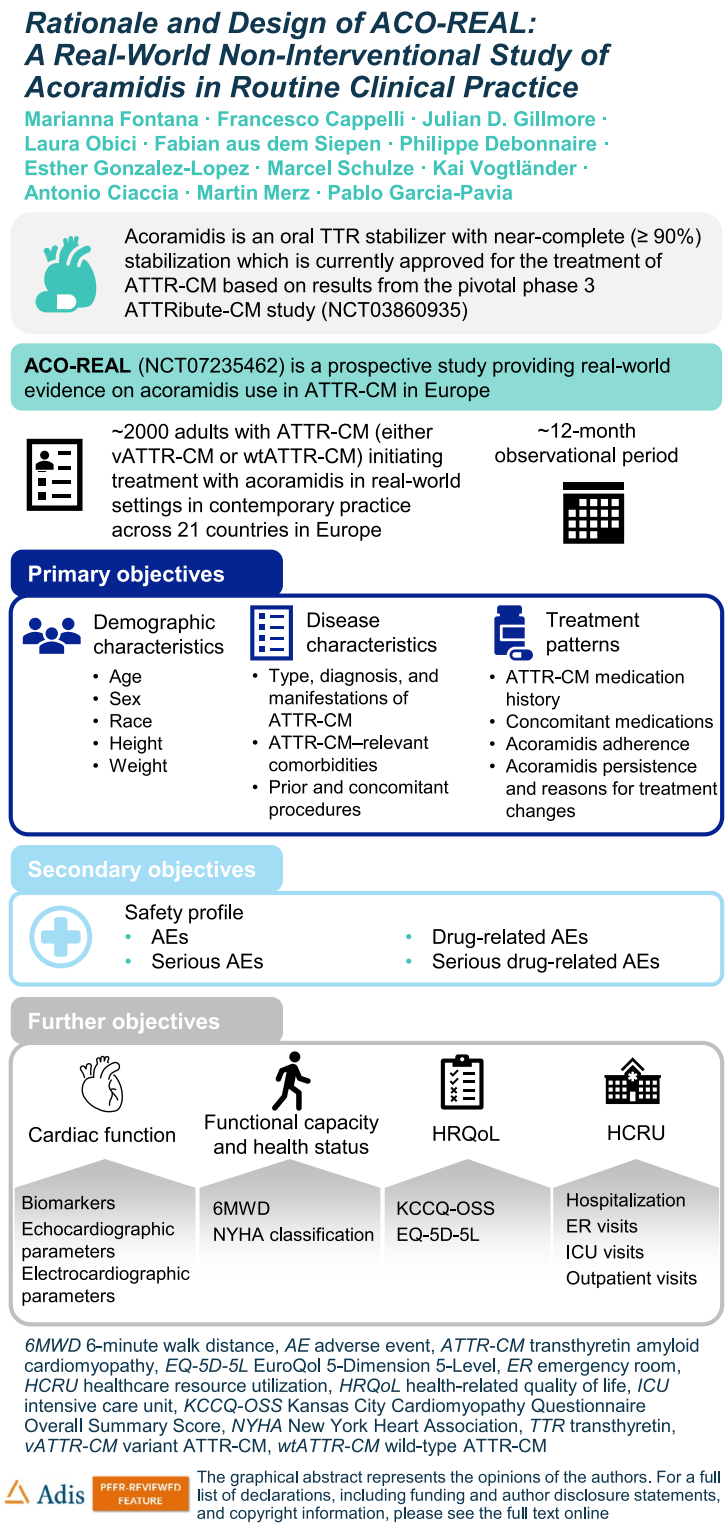
Conclusions: ACO-REAL is the first multinational observational study to collect regular, prospective, real-world data in participants with ATTR-CM treated with acoramidis. This study aims to provide insights into ATTR-CM treatment using real-world evidence from European healthcare systems and may help to guide decision-making in clinical practice. Graphical abstract available for this article.

Trial Registration: ClinicalTrials.gov identifier, NCT07235462

PLAIN LANGUAGE SUMMARY

Acoramidis is an oral drug that was approved for the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM), a type of heart disease, based on positive results from the ATTRibute-CM study (NCT03860935). This manuscript describes a new study, ACO-REAL (NCT07235462), that aims to provide information about acoramidis in patients in the real world. ACO-REAL is an ongoing study that is collecting data from participants over the course of 12 months who are receiving acoramidis to treat ATTR-CM. The study will include around 2000 participants from 21 European countries, and will focus on participant characteristics, treatments, reasons for any changes in treatment, and side effects. The study will assess participants' heart function, how the ATTR-CM disease changes over time, as well as participants' overall health and ability to function normally. The study will also assess quality of life and use of healthcare resources (such as hospital and emergency room visits). By analyzing data in a broad European population, this study should improve understanding of acoramidis use in patients with ATTR-CM in the real world, adding to data obtained from controlled clinical trials.

Graphical Abstract:



Keywords: Transthyretin amyloid cardiomyopathy; Acoramidis; Real-world; Study design; Treatment patterns

Key Summary Points

- ACO-REAL (NCT07235462) is an ongoing non-interventional study in Europe, which aims to generate real-world evidence on the use of acoramidis in transthyretin amyloid cardiomyopathy (ATTR-CM); acoramidis is an oral transthyretin stabilizer that achieves near-complete (≥ 90%) transthyretin stabilization.
- The primary objective of ACO-REAL is to assess the characteristics and treatment patterns in approximately 2000 participants with ATTR-CM receiving acoramidis across real-world settings over approximately 12 months.
- Data are being captured on the demographics; clinical characteristics; treatment patterns; adverse events; clinical course of participants treated with acoramidis, including cardiac function, functional capacity, health status, and health-related quality of life; and healthcare resource utilization.
- By analyzing these data in a broad and representative real-world population, the study has the potential to improve understanding of acoramidis use in routine clinical practice, to complement data from controlled clinical trials.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract to acilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.32764542.

INTRODUCTION

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, systemic disease characterized by the destabilization of transthyretin (TTR) tetramers into monomers, which misfold and accumulate as amyloid fibrils in the myocardium extracellular space [1, 2]. The wild-type form of ATTR-CM (ATTRwt-CM) most frequently affects older adults (>60 years, average age of approximately 75–80 years), with the exact causes unknown, while variant ATTR-CM (ATTRv-CM) is caused by variants in the *TTR* gene (age of onset varies between 30 and 80 years, depending on the mutation) [1–4]. The natural history of the disease includes progressive heart failure, arrhythmias, and repeated cardiovascular (CV) hospitalizations [1, 3, 5]. ATTR-CM is frequently underdiagnosed, leads to poor quality of life, and is fatal within 3–10 years if left untreated [3, 4].

The last decade has seen a significant shift toward improved outcomes for patients with ATTR-CM [2, 6]. This has been driven by the availability of effective ATTR-CM treatments, including TTR stabilizers (e.g., tafamidis, acoramidis), and *TTR* gene silencers (e.g., vutrisiran), in addition to advances in non-invasive diagnostic tools and increased awareness and understanding of the disease [2, 6–8]. In Europe, tafamidis became the first therapy approved for the treatment of ATTR-CM in 2020, followed by vutrisiran and acoramidis in 2025 [9–11]. However, access to these therapies varies by country due to differences in national healthcare systems and reimbursement policies. Furthermore, ATTR-CM remains an underrecognized cause of heart failure, and therapy initiation is still commonly delayed [5, 8].

Acoramidis is an oral TTR stabilizer that achieves near-complete (≥90%) TTR stabilization [12]. It is currently approved for the treatment of ATTRv-CM and ATTRwt-CM in the United States, European Union, Japan, United Kingdom, and Switzerland [13–17], based on results from the pivotal randomized controlled phase 3 ATTRibute-CM study (NCT03860935) [18]. In

ATTRibute-CM, at month 30, treatment with acoramidis led to a significantly better four-step hierarchical primary endpoint (all-cause mortality, CV-related hospitalization, change from baseline in N-terminal pro-B-type natriuretic peptide, and change from baseline in 6-min walk distance [6MWD]) versus placebo ($p < 0.001$) [18]. Acoramidis had a favorable safety profile, with a similar occurrence of adverse events (AEs) and a lower incidence of serious AEs compared with placebo [18].

Participants enrolled in clinical trials may not be representative of patients routinely encountered in clinical care [19]. Real-world studies can provide further clarity on treatment patterns and outcomes in routine clinical practice [20]. ACO-REAL (NCT07235462) is an ongoing non-interventional study that aims to generate real-world evidence on acoramidis use in the ATTR-CM population across Europe, complementing data from ATTRibute-CM. In this article, we describe the rationale and design of the ACO-REAL study.

METHODS

Study Design

ACO-REAL is an ongoing, prospective, multicenter, single-arm, observational study. ACO-REAL is being conducted in approximately 2000 participants initiating acoramidis for the treatment of ATTR-CM in real-world clinical settings. Participants are being enrolled from 135 sites across 21 European countries (Fig. 1).

Study Participants

Eligible participants are required to be aged at least 18 years and diagnosed with either ATTRwt-CM or ATTRv-CM. To ensure the observational nature of the study, the investigator's decision to initiate acoramidis must be made in accordance with routine clinical practice and independent of study participation; acoramidis must be initiated within 180 days after written informed consent is obtained. Participants taking part in interventional trials with experimental treatments outside of clinical practice, or those with contraindications to acoramidis, are excluded. A full list of eligibility criteria is included in Fig. 2. In calendar week 20 of 2026, the 400th participant was enrolled in ACO-REAL.

Study Objectives

The purpose of ACO-REAL is to capture data on the demographics, clinical characteristics, treatment patterns, AEs, and clinical course of participants treated with acoramidis. Data are collected during the approximately 12-month observational period from routine clinical visits and medical records and supplemented by telephone interviews. The primary censoring events include withdrawal of consent, loss to follow-up, death, or completion of the follow-up period.

The primary objective of ACO-REAL is to assess the characteristics and treatment patterns of participants with ATTR-CM receiving acoramidis across real-world settings in contemporary practice. Observations of the following are captured: demographic characteristics, including age, sex, race, height, and weight; clinical characteristics, including disease type (e.g., mixed phenotype [ATTR-CM and transthyretin amyloid polyneuropathy] and genetic status), diagnosis, and manifestations of ATTR-CM, ATTR-CM-relevant comorbidities, prior and concomitant procedures; general treatment patterns, including ATTR-CM-related medication history (e.g., TTR stabilizers and silencers) and concomitant medications; and acoramidis-specific treatment patterns, including adherence to acoramidis (defined as the proportion of days covered, based on the total number of days on acoramidis during the study), persistence of acoramidis (defined as the time to discontinuation of acoramidis), and reasons for treatment modifications, including switching from a different ATTR-CM medication to acoramidis and premature discontinuation or interruption of acoramidis.

The secondary objective is to describe the safety profile of acoramidis, which involves reporting AEs and drug-related AEs. In addition, ACO-REAL aims to evaluate the clinical course of ATTR-CM in patients initiating acoramidis

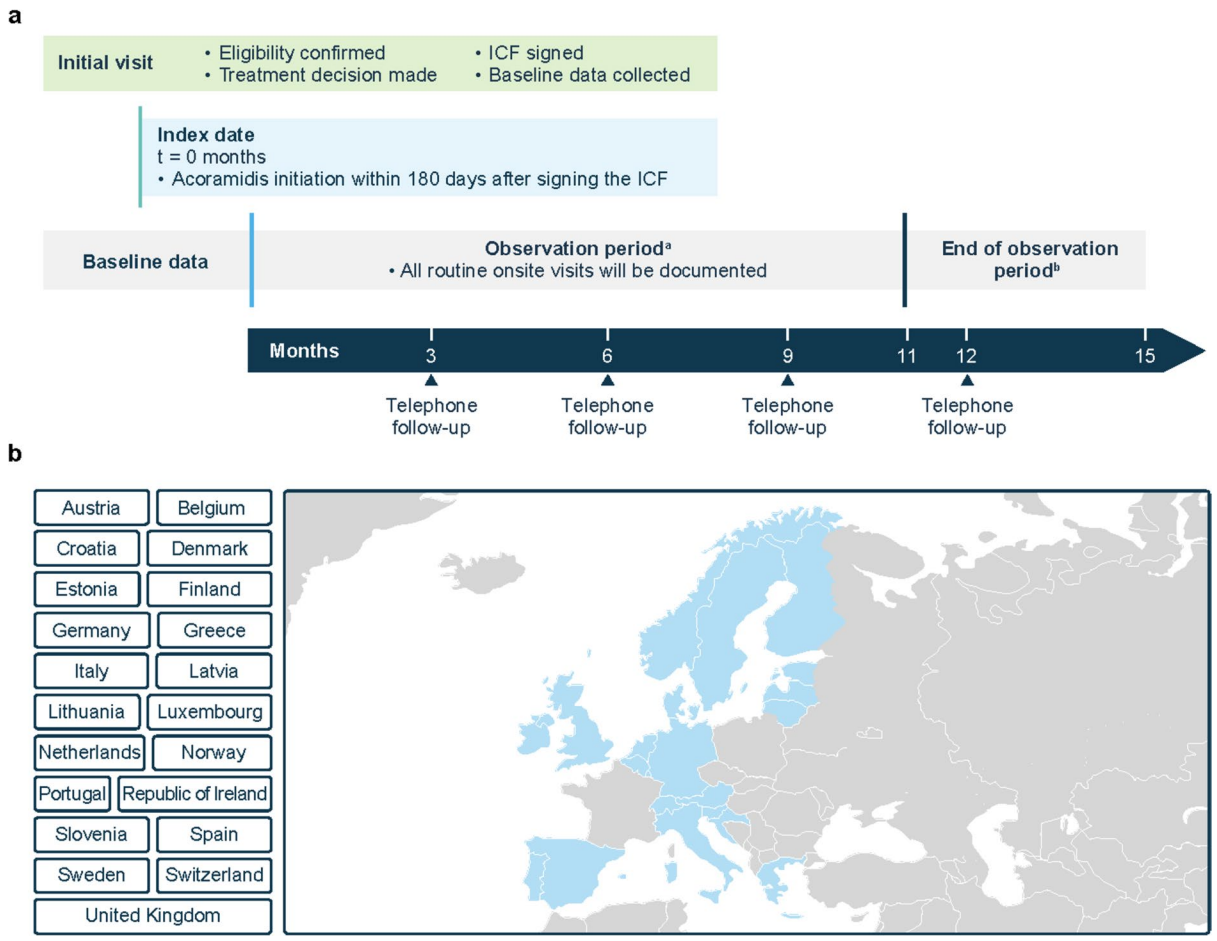


Fig. 1 ACO-REAL study design (**a**) and participating countries (**b**). [a]The observation period starts after acoramidis initiation; participants are observed for approximately 12 months. [b]A physical onsite visit between months 11 and 15 marks the end of observation; if none occurs, the month 12 telephone follow-up serves as the last documented visit. *ICF* informed consent form, *t* time

by capturing measurements related to cardiac function, functional capacity and health status, and health-related quality of life (HRQoL). Evaluation of cardiac function is being assessed through ATTR-CM-associated key biomarkers (e.g., N-terminal pro-B-type natriuretic peptide, serum TTR, high-sensitivity cardiac troponin T, and C-reactive protein), as well as echocardiographic and electrocardiographic parameters (including, but not limited to, left ventricular ejection fraction, left atrium dimension, left ventricular mass index, left ventricular end-diastolic interventricular septum thickness, left ventricular end-diastolic posterior wall thickness, and left ventricular global longitudinal strain, as available in routine clinical practice). Functional capacity and health status are captured through assessment of 6MWD and New York Heart Association classifications (as available in routine clinical practice). HRQoL is evaluated using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L). Healthcare resource utilization (HCRU) associated with acoramidis is also being evaluated. HCRU is described by recording ATTR-CM-related hospitalizations, ATTR-CM-related intensive care unit stays, emergency room visits, and outpatient visits.

A summary of primary, secondary, and further objectives is shown in Fig. 3.

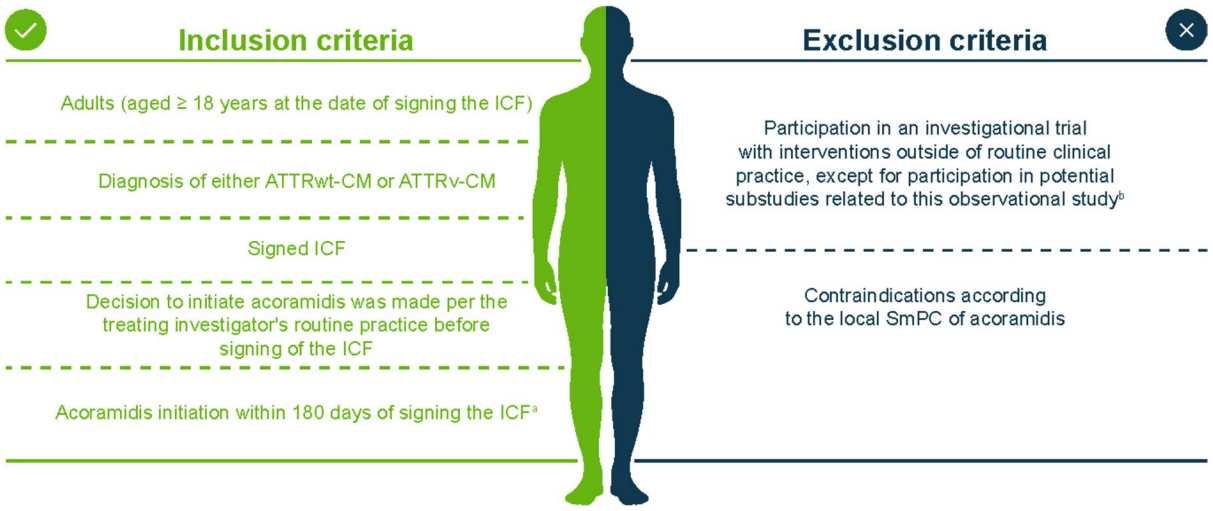


Fig. 2 Inclusion and exclusion criteria. [a]It was possible to initiate acoramidis on the same day as signing the ICF. [b]Participation in any separate substudy is voluntary and will be governed by separate protocols and informed consent processes. The main observational study does not include interventional procedures beyond routine clinical practice. *ATTRv-CM* variant transthyretin amyloid cardiomyopathy, *ATTRwt-CM* wild-type transthyretin amyloid cardiomyopathy, *ICF* informed consent form, *SmPC* summary of product characteristics

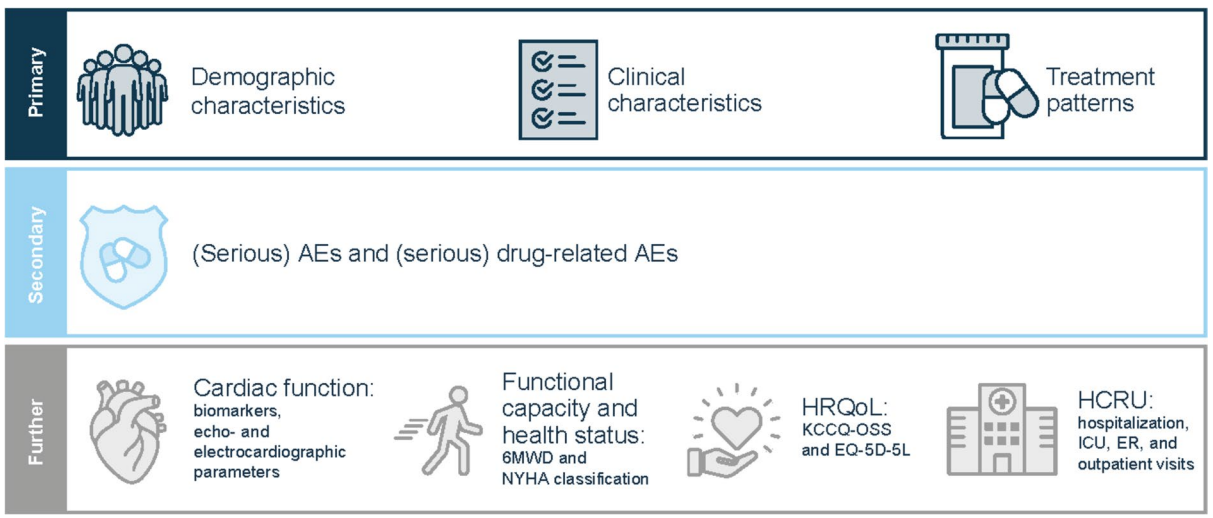


Fig. 3 ACO-REAL study objectives. *6MWD* 6-min walk distance, *AE* adverse event, *EQ-5D-5L* EuroQol 5-Dimension 5-Level, *ER* emergency room, *HCRU* healthcare resource utilization, *HRQoL* health-related quality of life, *ICU* intensive care unit, *KCCQ-OSS* Kansas City Cardiomyopathy Questionnaire Overall Summary score, *NYHA* New York Heart Association

Visits and Data Collection

Baseline data are collected during the initial visit, defined as the visit to the site during which the participant becomes eligible for enrollment. Follow-up visits occur during routine practice, typically once or twice per year. Data collected during follow-up visits include information

regarding treatment, AEs, cardiac function, functional capacity and health status, and HCRU. As participants typically visit the treating amyloidosis centers only once or twice per year, there is a risk of recall bias regarding events that may have occurred over an extended period. To minimize this risk of recall bias, quarterly telephone follow-ups are conducted throughout the study, at approximately months 3, 6, 9, and 12. During these follow-ups, participants are asked to complete the KCCQ and EQ-5D-5L questionnaires. Telephone follow-ups are also used, where needed, to obtain patient-reported information regarding concomitant medication, AEs, and other relevant clinical information.

An overview of the data collected during the study is included in Table 1. The planned observational period for participants is approximately 12 months after initiation of acoramidis, although this may be extended to 15 months to accommodate variability in site visits. The physical visit during months 11 or 12 marks the end of the observational period. If no physical visit occurs during months 11 or 12, a physical visit conducted anytime up to month 15 can be used as the last documented visit. If that is not possible, the telephone call conducted at month 12 is considered the last documented visit. In cases of premature treatment discontinuation, participants are followed to document any AEs for up to 6 days following the last acoramidis dose and reasons for discontinuation are recorded. Data regarding participants who switch to another therapy during this time period will also be recorded.

Data Analysis

Statistical analyses will be descriptive, with no pre-defined hypotheses. The sample size was determined due to feasibility reasons in a rare disease; a 50% incidence proportion maximizes the width of a confidence interval and a maximum of 2000 participants will not exceed a 95% confidence interval width of 4.43. The study aims to include a representative sample of study sites and a consecutive sampling approach is being applied to reduce selection bias by the treating investigators or their delegates; the sample of study sites will reflect the distribution of ATTR-CM (wild-type or variant) treatment settings in each participating country in the background of the specific local health system. Categorical variables will be presented as frequencies, and continuous variables as sample statistics. Repeated measurements will be assigned to an artificial visit scheme that assumes visits every 3 months. Missing data will be displayed but not imputed. For important data such as date of disease diagnosis and start and stop dates for prior and/or concomitant medications and adverse events, incomplete or missing data will be imported by a pre-specified algorithm. For example, a missing diagnosis day will be treated as the 15th day of the known month and if both the day and month are missing then it will be imputed as mid-year (June 30th). For missing dates of medications and adverse events, a missing day will be imputed as the first day of the known month; if both the month and day are missing, January 1 will be imputed as the date. Analyses will be conducted for the full analysis set and by country if participant numbers allow. The full analysis set includes all participants who took at least one acoramidis dose. Where possible, data will be stratified by subgroup (e.g., age, sex, and other baseline characteristics, including KCCQ, National Amyloidosis Centre staging criteria, and N-terminal pro-B-type natriuretic peptide).

Ethical Approval

In all countries where reference to an independent ethics committee (IEC) or institutional review board (IRB) is required, documented approval from appropriate IECs/IRBs is obtained for all participating centers prior to study start. All participants are required to provide informed consent before documentation of any data. The sponsor licensed the use of the KCCQ and EQ-5D-5L questionnaires with permission to publish the research results.

Table 1 Overview of data collected during the study

	Initial visit	Follow-up visit(s) (including end of observation[a])	Follow-up by telephone
HCP-reported			
Date/type of visit	X	X	X
Eligibility/informed consent	X		
Demographics	X		
ATTR-CM type and diagnostic characteristics	X		
ATTR-CM manifestations	X	X	X
Previously managed/resolved comorbidities	X[b]		
Laboratory values (if available)	X[c]	X	
Echocardiography parameters (if available)	X[c]	X	
Electrocardiography parameters (if available)	X[c]	X	
NYHA classification (if applicable)	X[c]	X	
6MWD (if available)	X[c]	X	
Primarily HCP-reported[d]			
Ongoing comorbidities	X	X	X
Prior and concomitant procedures	X	X	X
Previously administered ATTR-CM-related medications	X[b]		
Concomitant medications	X	X	X
Date of acoramidis initiation	X[e]		
Date(s) of acoramidis interruption/discontinuation (if applicable)		X	X
Reason(s) for switching to acoramidis (if applicable)	X		
Reason(s) for acoramidis interruption/discontinuation		X	X
Acoramidis prescriptions (date, refill prescription date)	X	X	X
Previous HCRU (hospitalization, ICU stays, ER visits, outpatient visits)	X[b]		
HCRU (hospitalization, ICU stays, ER visits, outpatient visits)		X	X
AEs (including reason, frequency and duration of hospitalizations due to cardiovascular events)	X[f]	X[g,h]	X[g,h]
Patient-reported			
HRQoL (KCCQ, EQ-5D-5L)	X		X

[a]The aim is to capture at least one onsite follow-up visit for each participant between the start of month 11 and end of month 15 after acoramidis initiation if treatment is still ongoing at the end of the observation. However, if no physical visit is scheduled between the months 11 and 15, the telephone call conducted at month 12 is considered the last documented visit

[b]The data collected at the initial visit may include information from up to 12 months before the initiation of acoramidis but after ATTR-CM diagnosis

Table 1 continued

[c]The data collected at the initial visit should be as recent as possible and must not be older than 12 months

[d]The preference is for the data to be sourced from medical records or clinical observation. However, this may be supplemented by patient-reported information obtained during follow-up phone calls, in which participants may report on co-medication, AEs, and other relevant clinical information

[e]The date of acoramidis initiation is recorded during the initial visit and may be reconfirmed at the subsequent follow-up, either onsite or via telephone

[f]Nontreatment-emergent

[g]Treatment-emergent

[h]For participants with premature acoramidis discontinuation, AEs are followed up for up to 6 days after the last treatment with acoramidis

6MWD 6-min walk distance, *AE* adverse event, *ATTR-CM* transthyretin amyloid cardiomyopathy, *EQ-5D-5L* EuroQol 5-Dimension 5-Level questionnaire, *ER* emergency room, *HCP* healthcare professional, *HCRU* healthcare resource utilization, *HRQoL* health-related quality of life, *ICU* intensive care unit, *KCCQ* Kansas City Cardiomyopathy Questionnaire, *NYHA* New York Heart Association

DISCUSSION

Considerable strides have been made to improve ATTR-CM care, aided by advances in diagnostic tools and heart failure management [2, 6]. In addition, the regulatory approvals of disease-modifiers acoramidis and vutrisiran have expanded the range of therapeutic possibilities for patients with ATTR-CM, for whom tafamidis was previously the only available treatment [7]. However, advances in care inevitably prompt new questions on how to optimize treatment decision-making in routine practice [2]. Real-world evidence can help to address these questions, as well as build on data from clinical trials in a broader population representative of routine clinical care [19].

Given that the efficacy and safety of acoramidis have been demonstrated in the ATTRibute-CM clinical trial [18], there is a desire to understand its impact in routine clinical practice beyond the controlled environment of clinical trials. Through the generation of real-world evidence on acoramidis in Europe, ACO-REAL aims to analyze participant characteristics, treatment patterns, and the safety of acoramidis in a broad population of participants with ATTR-CM to complement data from the ATTRibute-CM study, and add to the real-world evidence base in ATTR-CM generated by other observational studies to help to inform clinical guidelines and patient management strategies [21–23].

Strengths and Limitations

ACO-REAL is the first multinational observational study in participants with ATTR-CM treated with acoramidis to collect regular, prospective, real-world data on cardiac function, functional capacity and health status, and HRQoL. Improved survival rates have been observed in patients with ATTR-CM treated with TTR stabilizers in recent studies; however, real-world data are still lacking. In THAOS (NCT00628745), a phase 4, global, longitudinal, observational study, the 42-month survival rate was 77% among participants with ATTR-CM treated with tafamidis [21]. By contrast, a multicenter observational study in the United States (US) reported a survival rate of 61% at a median of 43 months among participants with ATTR-CM treated with tafamidis [22]. The difference in survival rates between these studies may be explained by differences in inclusion criteria, with the US study including a larger proportion of Black participants and participants with ATTRv-CM [22], and highlights the need for further real-world studies to provide clarity on the burden and disease course of ATTR-CM.

In addition to ACO-REAL, future real-world evidence is anticipated from ANTHOLOGY, an ongoing ATTR amyloidosis program that comprises two multi-country, longitudinal, observational studies: OverTTure (NCT06355934) and MaesTTRo (NCT06465810). The program aims to provide data on ATTR amyloidosis epidemiology, treatment patterns, disease outcomes, HCRU, and HRQoL [23]. These data will help to identify and address barriers to early diagnosis, as well as inform the development of guidance for improving patient care [23].

There is a need for evidence-based ATTR-CM therapeutic guidance on: (1) the potential for individualized treatment based on patient-level characteristics, and (2) switching between treatments [2]. These questions remain unanswered, partially due to the lack of head-to-head studies in this field, as well as challenges associated with comparing trial results due to variance in included populations [2, 7]. The primary objective of ACO-REAL is to assess the characteristics and treatment patterns of participants receiving acoramidis, including the incidence and reasons for switching from a different ATTR-CM medicine to acoramidis. These data may help to answer the question of whether switching to acoramidis benefits patients with a suboptimal response to other ATTR-CM treatments.

Given the observational design of ACO-REAL and limitations inherent to observational studies, findings generated will be subject to biases, such as selection bias, limitations to the availability of historical medical data, and differences in treatment or reporting owing to local guidelines and practices. As this is a single-arm study, the results cannot be directly compared with a control group within the same study population (limiting the ability to contextualize findings) and the study will not be able to establish a causal relationship between switching to acoramidis and improved outcomes in patients with a suboptimal response to prior therapies. Although the study aims to include patients from a variety of geographic regions, and from multiple sites within each country of varying size, there may be local limitations that reduce patient representation, such as access to recruiting investigators (including differences in patient profile in specialized sites vs. local general practice), acoramidis availability and reimbursement, and decisions relating to local standard of care. There may be variability in data coverage across different sites within the healthcare system, which could lead to inconsistencies or gaps in available data. Additionally, the infrequency of participant visits may impact the granularity of the data. However, quarterly telephone interviews are being implemented as a mitigation measure. Another limitation is the potential for recall bias, particularly when relying on patient-reported information during follow-up appointments. Participants may have difficulty accurately recalling dates of medication initiation or discontinuation, as well as adherence (e.g., the number of days in which they missed doses), which could affect the reliability of these data.

CONCLUSIONS

ACO-REAL is an ongoing, prospective, observational study of acoramidis, a TTR stabilizer that achieves near-complete TTR stabilization, in participants initiating treatment for ATTR-CM in real-world clinical settings. By analyzing participant clinical characteristics, treatment patterns, cardiac function, functional capacity and health status, HRQoL, and HCRU outcomes in a broad and representative real-world population in Europe, the study intends to improve understanding of acoramidis use in routine clinical practice beyond the controlled environment of clinical trials.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Marianna Fontana has acted as a consultant, advisor, or speaker for Akcea Therapeutics, Alexion Pharmaceuticals, Alnylam Pharmaceuticals, AstraZeneca, Eidos Therapeutics (a BridgeBio company), Intellia Therapeutics, Ionis Pharmaceuticals, Janssen Global Services, Novo Nordisk, and Pfizer; and has received research grants from Eidos Therapeutics (a BridgeBio company) and Pfizer. Francesco Cappelli reports personal fees from Pfizer, Alnylam Pharmaceuticals, BridgeBio, AstraZeneca, Novo Nordisk, Bristol Myers Squibb, and Bayer. Julian D. Gillmore has received consultancy fees from Pfizer, Ionis Pharmaceuticals, Attralus, Eidos Therapeutics (a BridgeBio company), Alnylam Pharmaceuticals, Alexion Pharmaceuticals, AstraZeneca, and Intellia Therapeutics; and has received institutional research grants from Alnylam Pharmaceuticals, AstraZeneca, Bayer, and Pfizer. Laura Obici reports speaker and consultancy fees from Bayer, BridgeBio, AstraZeneca, Alnylam Pharmaceuticals, Novo Nordisk, Intellia Therapeutics, Medison, Purpose Pharma, and Pfizer. Fabian aus dem Siepen reports advisory honoraria, speaker's honoraria, and travel grants from Alexion, Alnylam Pharmaceuticals, Bayer, Novo Nordisk, Neurimmune, and Pfizer; and he serves as principal investigator in trials sponsored by Alnylam Pharmaceuticals, AstraZeneca, Bayer, Intellia Therapeutics, Neurimmune, and Novo Nordisk. Philippe Debonnaire reports speaker and consultancy fees from Bayer, Pfizer, AstraZeneca, and Alnylam Pharmaceuticals, and research funding from Pfizer and AstraZeneca. Esther Gonzalez-Lopez reports speaking fees from Pfizer, Eidos Therapeutics (a BridgeBio company), Bayer, AstraZeneca and Alnylam Pharmaceuticals; and consulting fees from Pfizer, Alnylam Pharmaceuticals, Bayer, Akcea, Novo Nordisk, AstraZeneca, and Proclara. Marcel Schulze, Kai Vogtländer, Antonio Ciaccia, and Martin Merz are employees and stockholders of Bayer. Pablo Garcia-Pavia has received speaker fees from Alnylam Pharmaceuticals, AstraZeneca, Bayer, Eidos Therapeutics (a BridgeBio company), Intellia Therapeutics, Ionis Pharmaceuticals, Novo Nordisk, and Pfizer; has received consulting fees from Alexion Pharmaceuticals, Alnylam Pharmaceuticals, AstraZeneca, Attralus, Bayer, BridgeBio, Intellia Therapeutics, Ionis Pharmaceuticals, Pfizer, Neuroimmune, and Novo Nordisk; and has received research/educational support to his institution from Alnylam Pharmaceuticals, AstraZeneca,

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Ethical Approval. In all countries where reference to an IEC or IRB is required, documented approval from appropriate IECs/IRBs is obtained for all participating centers prior to study start. All participants are required to provide informed consent before documentation of any data. The sponsor licensed the use of the KCCQ and EQ-5D-5L questionnaires with permission to publish the research results.

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